Gender differences in presentation, management and inhospital outcome in patients with ST-segment elevation myocardial infarction: data from 5000 patients included in the ORBI prospective French regional registry.

Guillaume Leurent, Ronan Garlantézec, Vincent Auffret, Jean Philippe Hacot, Isabelle Coudert, Emmanuelle Filippi, Antoine Rialan, Benoît Moquet, Gilles Rouault, Martine Gilard, et al.

Title: Gender differences in presentation, management and in-hospital outcome in patients with ST-elevation myocardial infarction. Data from 5,000 patients included in the ORBI prospective French regional registry.

Titre: Différences liées au genre dans la présentation, la gestion et le devenir intra hospitalier des patients hospitalisés pour syndrome coronaire aigu avec sus-décalage persistant du segment ST. Analyse des données de 5000 patients inclus dans le registre prospectif français ORBI.

Short title: Gender differences in STEMI.

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Mots clés: genre, différences, syndrome coronaire aigu avec sus-décalage persistant du segment ST, interaction âge-genre, pronostic ; mortalité

This paper is not under consideration elsewhere.

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Abstract:

Background: Gender differences in presentation, management and outcome in patients with ST-elevation myocardial infarction (STEMI) are reported.

Aim: To determine whether female gender is associated with higher in-hospital mortality.

Methods: Data from ORBI, a regional STEMI registry of 5 years' standing, were analyzed. The main data for presentation, management, in-hospital outcome and prescription at discharge were compared between genders. Various adjusted hazard ratios were then calculated for in-hospital mortality (women vs. men).

Results: The analysis included 5,000 patients (mean age = 62.6 ± 13 years), with 1,174 women (23.5%). Women were a mean 8 years older than men, with more frequent co-morbidities. Median ischemia time was 215 minutes (26 minutes longer in women, $p<0.05$). Reperfusion strategies in women involved less fibrinolysis, coronary angiography, radial access and thrombo-aspiration. Female gender, especially in patients younger than 60 years, was associated with poorer in-hospital prognosis (including higher in-hospital mortality: 9% vs. 4% in men; $p<0.0001$), and under-utilisation of the recommended treatment at discharge. Moreover, excess female in-hospital mortality was independent of presentation, revascularisation time and reperfusion strategy (hazard ratio for women: 1.33, 95% confidence interval, 1.01 to 1.76; $p=0.04$).

Conclusions: One in 4 patients admitted for STEMI was female, with significant differences in presentation. Female gender was associated with less optimal treatment, both in the acute phase and at discharge. Effort should be made to reduce those differences, especially as female gender was independently associated with elevated risk of in-hospital mortality.

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Résumé:

Contexte: Des différences liées au sexe sont signalées dans la présentation, la gestion et le pronostic des patients hospitalisés pour infarctus du myocarde avec élévation du segment ST (IDM ST +).

Objectif: déterminer si le sexe féminin est associé à une mortalité intra-hospitalière plus élevée.

Méthode: Nous avons analysé les données d'ORBI, un registre régional de 5 ans concernant les IDM ST+. Les principales données concernant la présentation, la gestion, le devenir intra-hospitalier et le traitement à la sortie ont été comparées en fonction du sexe. Ensuite, nous avons analysé la mortalité intra hospitalière (femmes vs hommes), avec différentes variables d'ajustement.

Résultats: L'analyse a inclus 5000 patients (âge moyen = 62,6 ± 13 ans), dont 1174 femmes (23,5%), qui présentaient des co-morbidités plus fréquentes et étaient 8 ans plus âgées que les hommes. Le temps d'ischémie médian était de 215 minutes (26 minutes de plus chez les femmes). Comparativement aux hommes, les stratégies de reperfusion chez les femmes comportaient moins de fibrinolyse, de coronarographie, d'accès radial et de thrombo-aspiration. Le sexe féminin, en particulier chez les moins de 60 ans, était associée à un mauvais pronostic intra-hospitalier (y compris une plus forte mortalité intra hospitalière: 9% contre 4% chez les hommes, p <0,0001), et une sous-utilisation des traitements recommandés à la sortie. Par ailleurs, la surmortalité intra hospitalière observée chez les femmes était indépendante de la présentation, des délais de revascularisation et des stratégies de reperfusion (hasard ratio=1,33, intervalle de confiance 95% :1,01 à 1.76, p = 0,04).

Conclusions: Une personne sur 4 patients admis pour un IDM ST+ est une femme, avec des différences significatives dans la présentation. Le sexe féminin est associé à un traitement moins optimal, tant à la phase aiguë qu'à la sortie d'hôpital. Un effort particulier devra être

effectué afin de réduire ces différences, d'autant plus que le sexe féminin semble constituer dans cette analyse un risque indépendant de surmortalité intra-hospitalière.

Introduction: Several studies have reported increased in-hospital mortality in myocardial infarction (MI) with persistent ST-segment elevation (STEMI) in women[1-7]. Several hypotheses have been put forward to account for this excess female mortality, including more serious comorbidity, longer time to revascularization, or less "optimal" reperfusion strategies. It is, however, not yet clearly established whether female gender is in itself a risk factor for in-hospital death in case of STEMI. The present study is an update on gender-linked differences in the characteristics, means of treatment, mortality and in-hospital prognosis of patients admitted for STEMI.

Method: We used the data from the Brittany Regional Infarction Observatory (*Observatoire Régional Breton sur l'Infarctus*: ORBI)[8]. Brittany is an administrative Region with a population of 3.2 million and 9 interventional cardiology centers (see list in Appendix), for an area of 34,023 km². ORBI prospectively includes all patients admitted within 24 hours of symptom onset to any of the 9 centers for STEMI (final diagnosis). Demographic and electrocardiographic data, treatments, time intervals and in-hospital events are recorded prospectively. Overall ischemia time is defined as the time between symptom onset and initiation of reperfusion: balloon inflation, in case of primary angioplasty, or administration of fibrinolytic treatment. All patients registered by ORBI between July 1st, 2006 and August 31st, 2011 were included in the present study.

Statistical analysis: Qualitative data were expressed as percentages and quantitative data as means ± standard deviations, except for times, which were expressed as medians [range]. Multiple imputation was performed to take into account missing data[9] As a first step, univariate analysis according to gender, clinical characteristics, time to revascularization, revascularization strategy, in-hospital prognosis and discharge prescription was performed. Student (or Wilcoxon, as appropriate) and Chi² were used for quantitative and qualitative data

respectively. In a second step, in-hospital mortality was analyzed according to gender, using a Cox model. The association was presented in the form of a Hazard Ratio (HR) with 95% confidence intervals (95% CI). Various models were constructed according to adjustment strategy: model 1, non-adjusted; model 2, adjusted for patient characteristics (age, diabetes, arterial hypertension, active smoking, anterior STEMI location, 3-vessels or common left main coronaropathy); model 3, adjusted for the variables of model 2 and for overall ischemia time; and model 4, adjustment for the variables of model 3 and for revascularization parameters (coronarography, primary angioplasty, radial arterial approach, thrombo-aspiration, anti-Gp2b3a administration, fibrinolysis).

The significance threshold was systematically set at 5%. Statistical analysis used SAS® software, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results: Over the study period, 5,000 patients (mean age, 62.6 ± 13 years) were included in ORBI, with 1,174 (23.5%) female. The main patient characteristics and coronaropathy and MI data are presented according to gender in Table 1. Emergency myocardial revascularization was performed in 4,344 patients (87%): 3,583 (71%) by primary angioplasty and 761 (15%) by fibrinolysis.

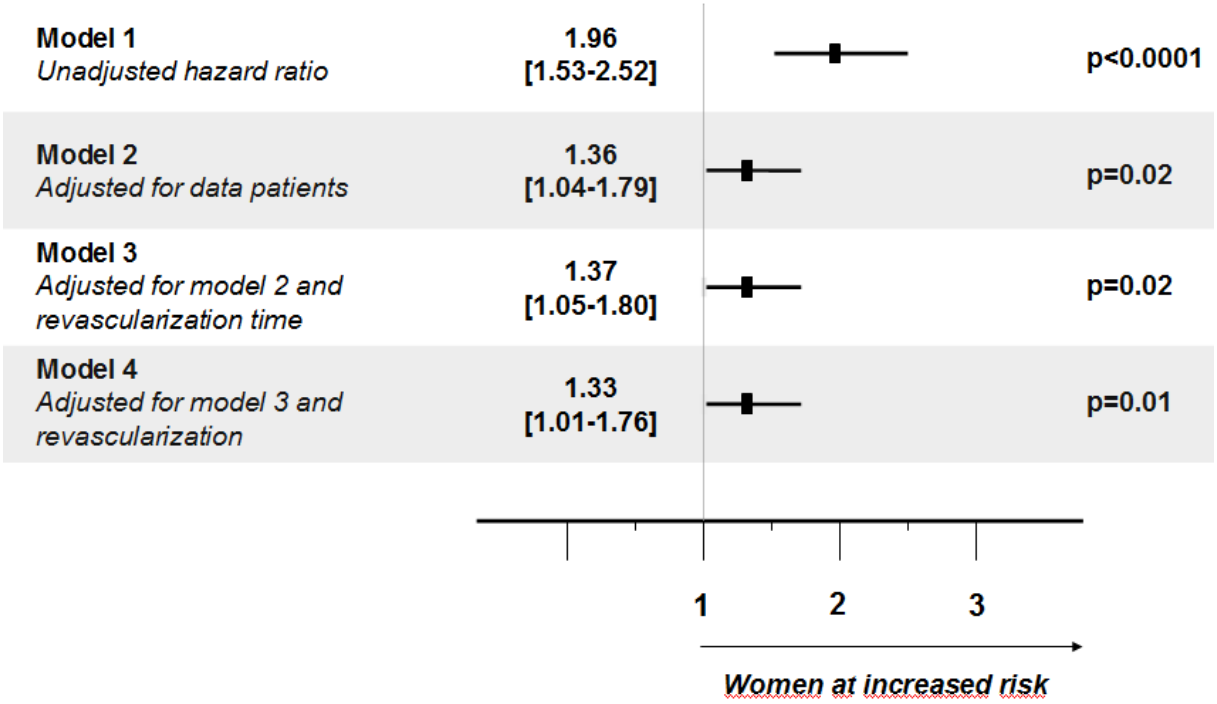
The initial emergency call was on the dedicated emergency telephone number 15 (emergency medicalized ambulance service: SAMU) for 40% of female versus 44% of male patients (p=0.004). ECG when performed before hospital admission showed significant ST-segment elevation in 88% of female versus 95% of male patients (p=0.03). The SAMU provided pre-admission treatment in 55% of female versus 61% of male patients (p<0.001). Finally, direct access to the cath lab in case of primary angioplasty was available for 57% of female versus 66% of male patients (p<0.0001).

Median overall ischemia time was 215 minutes [63-1,530 min], and was significantly longer for female patients (235 min, vs. 209 min for male patients, $p<0.05$), with delayed treatment at all stages: median pain-to-call time, 60 vs. 44 min ($p<0.0001$); call-to-door, 130 vs. 125 min ($p<0.05$); and door-to-balloon (or thrombo-aspiration) in primary angioplasty, 45 vs. 40 min ($p<0.05$). Thus the median time from first medical contact to balloon inflation or thrombo-aspiration was 95 min: 100 min in female vs. 94 min in male patients ($p<0.05$), and less than 120 min for respectively 65% and 72% ($p<0.0001$). Table 2 presents revascularization strategies according to gender, showing lower rates of use of the various reperfusion techniques in women.

In-hospital evolution: As seen in Table 3, in-hospital morbidity and mortality were significantly higher in women, with higher rates of high-grade atrioventricular block and atrial fibrillation and lower left-ventricle ejection fractions. Likewise, total hospital stay was longer. Above all, mortality from all causes was higher: 106 (9%) vs. 167 (4%) ($p<0.0001$). These deaths were mainly from cardiovascular causes: 96 (90% of deaths) in female and 149 (89%) in male patients. Death from hemorrhage was rare: n=11; 3 male versus 8 female ($p<0.001$), including 8 intracranial hemorrhages (2 male, 6 female; $p=0.002$) and 1 retroperitoneal hematoma (in a male patient). As seen in Table 4, which compares in-hospital mortality by age and gender, excess mortality mainly affected female patients under 60 years of age, in univariate analysis. Finally, the rate of hemorrhagic events of whatever severity, systematically screened in 427 patients, was 3% in female versus 2% in male patients ($p=0.48$).

Discharge treatment: Table 5 shows the rate of prescription of the various treatments recommended by the European Society of Cardiology[10] at discharge home, according to gender, again showing under-prescription for women in all cases.

Adjusted analysis of in-hospital mortality: Female STEMI patients showed significantly higher non-adjusted in-hospital mortality than males (model 1): HR = 1.96 [1.53-2.52]; p<0.0001. This excess mortality persisted after adjustment on patient characteristics (model 2): HR = 1.36 [1.04-1.79]; p=0.02. It also persisted after adjustment on time to revascularization (model 3): HR = 1.37 [1.05-1.80]: p=0.02. Finally, "complete" adjustment, on patient characteristics and time to revascularization and revascularization technique (model 4), gave an HR of 1.33 [95% CI, 1.01-1.76] (p=0.04), revealed excess female in-hospital mortality in STEMI, independently of all study parameters (figure 1).



Discussion

The present study highlights the specificities of STEMI and its prognosis in female patients: onset associated with higher comorbidity rates, later and less optimal treatment, and above all much poorer in-hospital prognosis, especially in younger women.

The present female prevalence for STEMI (about 1 in 4) is in full agreement with French national data[3, 11]. Likewise, the present rate of comorbidity in female patients is in agreement with recent registry reports[2], notably a higher mean age in females: 65.5 vs. 61.2 years in the American registry[7], 71 vs. 62 years in the German Mitra registry[12], and 67 vs. 56 years in the Korean registry[5].

Time to revascularization : ORBI revealed significantly longer ischemia times in women, due to less use of the SAMU emergency service, lower ECG input and longer delays to all types of treatment, as also found in other registries[13,14]. Thus, the median pain-to-door time in the American registry[13] was 195 min for women, versus 150 min for men, and 217 versus 161 min in the Korean registry[5]. Most notable was the significantly longer (by 16 min) pain-to-call time in the ORBI data, indicating a need for greater awareness of the issue of STEMI on the part of women and for early call for specialized help (SAMU) in case of chest pain, to allow direct admission to the cath lab[8, 10].

Management: The present study also found a very clear gender-related difference in coronary revascularization strategy. Here again, under-implementation of fibrinolysis and angioplasty in female patients has frequently been reported[5, 6, 12, 13, 15]. Most registries, however, fail to specify revascularization techniques, and data on arterial approach or thrombo-aspiration, for example, are seldom reported. The present study found significant differences in these two aspects of revascularization, yet recommended (European Society of Cardiology's guideline: IIa[10]): although of proven benefit in terms of mortality[16], the radial approach is less often used in female patients: 40% vs. 51%; $p<0.0001$. Likewise, despite proof of benefit[17], thrombo-aspiration is again less often used in women (46% vs. 55%; $p<0.0001$).

Prognosis: Poorer in-hospital prognosis for female STEMI patients has been frequently reported[1, 5-7, 18, 19]. The main contribution of the present study lies in its analysis of this excess female mortality, with a 2-fold greater rate of in-hospital death in women.

Firstly, it emerged that the excess mortality exclusively concerned younger women, being significant only in those under 60 years of age, with a trend in 60-to-70 year-olds; in older female patients, no differential mortality was found. This age-gender interaction was also observed in the American registry[7], with post-STEMI in-hospital mortality 98% greater in 50 year-old women than in men of the same age, but identical in both sexes after 80 years: 12.2% in female and 12.3% in male patients. This is an especially worrying factor as a recent analysis of French STEMI data found a constant increase in the proportion of young women in the STEMI population over the last 15 years: 11.8% of women were aged less than 60 years in 1995, versus 25.5% in 2010 ($p<0.001$)[3].

Moreover, it emerged that this excess mortality was not simply due to greater comorbidity (model 2), longer time to revascularization (model 3) or revascularization strategies that were less "aggressive" and less in line with scientific recommendations (model 4). Rather, female gender as such emerged as a factor of elevated risk of in-hospital mortality. Few registries have undertaken such analysis of the female in-hospital mortality they display. However, an analysis of the Korean data, using a methodology similar to the present study, showed that the excess female mortality that persisted after adjustment on age became non-significant when adjusted on age, medical history, hemodynamic status and "clinical performance"[5]. A previous analysis of data from the State of New York registry also showed significant excess mortality in under-75 year-old women that disappeared after adjustment on age, comorbidity and hemodynamic status[20]. Likewise, a recent report from a French registry also highlighted an impact of the age-gender interaction, but with higher hospital mortality in the subgroup of over-65 year old women[21]. This monocentric registry studied 2600 patients (including 199 under-65 year-old women) in a 23 years period. Therefore, the impact of this age-gender interaction is different according to the inclusion period. One quality of our multicentric

registry is the inclusion of a high number of patients, in a quite short period, with homogenous STEMI-support.

We have no clear explanation for this excess female mortality. It has been suggested that, in STEMI, pre-hospital mortality is higher in male subjects[22], counterbalancing the excess female in-hospital mortality. It is also established that young women enjoy hormonal protection against atherosclerosis[23]; it may thus be the case that pre-menopausal women admitted for STEMI are those with especially severe atherosclerosis or in whom risk factors are accumulated. Moreover, as young women show less stenosis in the coronary network than men, they develop a lower ischemic myocardial protection response, entailing greater vulnerability to acute ischemia[24]. And finally, the mechanism of coronary occlusion may vary according to age, with plaque erosion predominating in younger subjects and rupture in the over-50 year-olds[25].

Study limitations: As ORBI is a specifically French registry, the present findings may not be extrapolated elsewhere. Moreover, ORBI is by definition restricted to patients admitted to an interventional cardiology center, and this may induce selection bias: STEMI cases managed medically in a non-interventional setting are not included. It is, however, unlikely that women are referred differently from male patients of the same age group.

Conclusion

The present analysis of ORBI registry data found that about a quarter of patients admitted for STEMI were female, with a significantly greater rate of comorbidity than in men. Moreover, time to revascularization was significantly longer, partly due to women delaying their call for medical help, and treatment strategies were less optimal, both in the acute phase and at discharge. Women, and especially younger women, thus show excess in-hospital mortality that is only partly accounted for by the above factors and persists after adjustment.

It would therefore seem necessary to raise awareness of the issue: in the female population in particular, but also in emergency staff and cardiologists. Only management that is at least as "optimal" for women as for men can bring down this mortality rate.

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APPENDIX

The following medical centres participated in this study

Centre Hospitalier Universitaire de Rennes; Clinique Saint Laurent, Rennes; Centre Hospitalier de St Malo; Centre Hospitalier de St Brieuc; Centre Hospitalier de Lorient; Centre Hospitalier de Vannes; Centre Hospitalier Universitaire de Brest; Centre Hospitalier de Quimper; Clinique du Grand Large, Brest.

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Table 1: Main patient characteristics according to gender.

	Male (n=3,826)	**Female** (n=1,174)	**p**
Age	60.8 ±12	68.8 ±14	**<0.001**
Arterial hypertension	1,377 (36%)	634 (54%)	**<0.001**
Dyslipidemia	1,989 (52%)	528 (45%)	**<0.001**
Diabetes	420 (11%)	152 (13%)	0.06
Active smoking	1,568 (41%)	305 (26%)	**<0.001**
Body-mass index (kg/m²)	26.8 ±3	25.5 ±5	**<0.001**
Known coronaropathy	734 (19%)	208 (18%)	0.2
History of myocardial infarction	306 (8%)	47 (4%)	**<0.001**

Anterior STEMI location	1,606 (42%)	537 (45%)	**0.02**
3-vessels or common left main coronaropathy	700 (18%)	183 (15%)	**0.03**
Killip III or IV at admission	182 (5%)	92 (8%)	**<0.001**

Table 2: Univariate analysis of coronary revascularization techniques according to patient gender

		Male (n=3,826)	Female (n=1,174)	p
Primary strategy	**Fibrinolysis**	618 (16%)	143 (12%)	**0.0009**
	Primary angioplasty	2,754 (72%)	829 (70%)	**0.36**
	No acute-phase reperfusion:	454 (12%)	203 (18%)	**<0.0001**
	- **no acute-phase coronarography**	229 (6%)	107 (9%)	
	- **acute-phase coronarography without angioplasty**	178 (5%)	90 (8%)	
	- **acute-phase coronarography with delayed angioplasty**	47 (1%)	5 (<1%)	
Anti-Gp2b3a		2,269 (59%)	628 (53%)	**0.0004**
Coronarography (at admission or otherwise)		3,772 (98%)	1,122 (95%)	**<0.0001**
Radial approach*		1,348 (51%)	303 (40%)	**<0.0001**
Thrombo-aspiration**		1,433 (55%)	388 (46%)	**<0.0001**
Stent**		2,188 (85%)	649 (78%)	0.4
Drug Eluting Stent**		319 (12%)	99 (12%)	0.8
TIMI 3 flow (spontaneous, after fibrinolysis or at end of angioplasty)†		2,555 (91%)	758 (82%)	**0.02**

*percentage of coronarography patients with data available (n=2,618 male, 743 female).
** percentage of primary angioplasty patients.
† percentage of acute-phase coronarography patients (n=2,799 male, 924 female).

Table 3: In-hospital outcome according to gender

	Male (n=3,826)	Female (n=1,174)	p
Atrial fibrillation	138 (3%)	82 (7%)	**<0.0001**
High-grade atrioventricular block	112 (3%)	68 (6%)	**<0.0001**
Total hospital stay (days)	6.7 ±4	7.6 ±4	**<0.0001**
Left ventricle ejection fraction (%, on echocardiography)	50.5 ±10	49.4 ±11	**0.004**
Mortality	167 (4%)	106 (9%)	**<0.0001**
Mortality from cardiovascular causes, Including:	149 (4%)	96 (8%)	**<0.0001**
- cardiogenic shock	60	41	
- mechanical complication	30	26	
- arrhythmia/conduction disorder	30	18	

Table 4: Mortality according to age group and gender.

Deaths	Men	Women	Total	p-value
Age < 60 yrs	34/1,844 (1.8%)	13/317 (4.1%)	47/2,161 (2.1%)	**0.01**
60 ≤ age < 70	32/930 (3.4%)	12/202 (5.9%)	44/1,132 (3.9%)	0.09
70 ≤ age < 80	54/743 (7.2%)	23/332 (6.9%)	77/1,075 (7.1%)	0.84
80 ≤ age	47/308 (15.2%)	58/323 (17.9%)	105/631 (16.6%)	0.36

Table 5: Discharge prescription according to gender, for patients discharged alive from the hospital

	Male (n=3,659)	**Female (n=1,068)**	**p**
Aspirin	3,584 (98%)	1,022 (95%)	**<0.0001**
Clopidogrel/Prasugrel	3,506 (96%)	993 (93%)	**<0.0001**
Beta-blockers	3,349 (91%)	940 (88%)	**0.001**
Angiotensin conversion enzyme inhibitor/Sartan	2,481 (67%)	662 (62%)	**<0.0001**
Statin	3,475 (95%)	955 (89%)	**<0.0001**
Cardiovascular rehabilitation	1,577 (43%)	267 (25%)	**<0.0001**